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{q1}Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

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A list of the TRIDENT-1 investigators is provided in the Supplementary Appendix,{q3} available at NEJM.org.

Abstract{q4}

Background

The ROS1{q5} tyrosine kinase inhibitors (TKIs) currently approved for the treatment of *ROS1* fusion–positive non–small-cell lung cancer (NSCLC) have antitumor activity, but resistance develops in tumors, and intracranial activity is

suboptimal. Repotrectinib is a next-generation ROS1 TKI with preclinical activity against *ROS1* fusion–positive cancers with resistance mutations such as *ROS1* G2032R.

Methods

In this registrational phase 1–2 trial, we assessed the efficacy and safety of repotrectinib in patients with advanced solid tumors, including *ROS1* fusion–positive NSCLC. The primary efficacy end point in the phase 2 trial was confirmed objective response,{q6} and antitumor activity analysis combined phase 1 and 2 results. Duration of response, progression-free survival, and safety were secondary end points in phase 2.

Results

On the basis of results from the phase 1 trial, the recommended phase 2 dose of repotrectinib was 160{q7} mg daily for 14 days, followed by 160 mg twice daily. Response occurred in 56 of the 71 patients (79%; 95% confidence interval [CI], 68 to 88) with *ROS1* fusion–positive NSCLC who had not previously received a ROS1 TKI; the median duration of response was 34.1 months (95% CI, 25.6 to could not be estimated), and median progression-free survival was 35.7 months (95% CI, 27.4 to could not be estimated). Response occurred in 21 of the 56 patients (38%; 95% CI, 25 to 52) with *ROS1* fusion–positive NSCLC who had previously received one ROS1 TKI and had never received chemotherapy; the median duration of response was 14.8 months (95% CI, 7.6 to could not be estimated), and median progression-free survival was 9.0 months (95% CI, 6.8 to 19.6). Ten of the 17 patients (59%; 95% CI, 33 to 82) with the *ROS1* G2032R mutation had a response. A total of 426 patients received the phase 2 dose; the most common treatment-related adverse events were dizziness (in 58% of the patients), dysgeusia (in 50%), and paresthesia (in 30%), and 3% discontinued repotrectinib owing to treatment-related adverse events.

Conclusions

Repotrectinib had durable clinical activity in patients with *ROS1* fusion–positive NSCLC, regardless of whether they had previously received a ROS1 TKI. Adverse events were mainly of low grade and compatible with long-term administration. (Funded by Turning Point Therapeutics; TRIDENT-1 ClinicalTrials.gov number, NCT03093116{q8}.)

ROS1 fusions are oncogenic drivers that occur in up to 2% of patients with non–small-cell lung cancer (NSCLC).[1] The currently approved ROS1 tyrosine kinase inhibitors (TKIs), crizotinib and entrectinib, present two major challenges.[2] First, acquired resistance mutations develop in at least 50% of patients treated with these agents and limit the durability of the response.[3,4] Neither drug is active against recalcitrant *ROS1* mutations, such as the solvent-front mutation G2032R{q10},[2] that are commonly acquired during treatment with any of several ROS1 TKIs,[3,4] which include lorlatinib,[5] a potential therapeutic option after crizotinib or entrectinib.

Second, intracranial activity can be suboptimal, and brain metastases are common in patients with *ROS1* fusion–positive NSCLC.[2] Treatment{q11} with crizotinib results in a low concentration in the cerebrospinal fluid,[6] and disease progression in approximately half the patients treated with crizotinib first occurs in the central nervous system (CNS).[7] Although{q12} entrectinib provides improved CNS coverage as compared with crizotinib, only 11% of patients with disease progression limited to the CNS during previous crizotinib therapy had a response to entrectinib.[8]

A TKI is needed that addresses both challenges. Repotrectinib is a next-generation ROS1 and TRK TKI.[9] Owing to its compact macrocyclic structure, repotrectinib has a small tyrosine kinase–binding interface. This{q13} characteristic allows repotrectinib to circumvent steric hindrance from *ROS1* resistance mutations, which, in contrast to other ROS1 TKIs, enables the potent inhibition of both wild-type and G2032R-mutant *ROS1* fusions.[9,10] In addition, repotrectinib was designed to enhance the intracranial activity of the drug: repotrectinib led to greater shrinkage of brain tumors and longer survival than entrectinib in a patient-derived *ROS1* fusion–positive intracranial model.[11]

TRIDENT-1 is{q14} an ongoing international, registrational phase 1–2 trial evaluating repotrectinib in patients with advanced, fusion-positive cancers. Here, we report the efficacy of repotrectinib in patients with *ROS1* fusion–positive NSCLC (phase 1–2) and the safety of repotrectinib in patients treated at the recommended phase 2 dose.

Methods

Trial Design and Treatment

In the phase 1 trial, which was conducted at eight sites across three countries, we enrolled patients with locally advanced or metastatic solid tumors harboring *ROS1*, *NTRK*1–3, or *ALK* gene fusions. We{q15} assessed multiple doses and schedules of repotrectinib to establish the phase 2 dose.

In the phase 2 trial, which was conducted at 152 sites across 19 countries, we enrolled patients in six cohorts defined on the basis of the molecular characteristics of the tumors and the treatment history of the patients. Four of the cohorts were composed of patients with *ROS1* fusion–positive NSCLC, which is the focus of the current article. All the patients in the other two cohorts had *NTRK* fusion–positive solid tumors and were included in the safety analysis population. The design of the TRIDENT-1 trial is provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

In the phase 2 trial, all the enrolled patients were{q16} assigned to receive repotrectinib until progression of disease, onset of unacceptable toxic effects, or withdrawal of consent. The dose-escalation methods in phase 1 and the dose-escalation criteria in phase 2 are described in the Supplementary Appendix.

Trial Oversight

Turning Point Therapeutics, a wholly owned subsidiary of Bristol-Myers Squibb, sponsored and designed the trial with input from the investigators. As part of the site agreement, the investigators agreed to keep all aspects and outcomes of the trial confidential. The trial was conducted in accordance with the appropriate {q17}Food and Drug Administration regulations and the International Council for Harmonisation E6 guideline for Good Clinical Practice. The protocol (available at NEJM.org) was reviewed by the appropriate health authorities and institutional committees. All the patients provided written informed consent. The clinical safety committee (in phase 1), the data{q18} monitoring committee (in phase 2), and Turning Point Therapeutics provided trial oversight. All the authors participated in the interpretation of the data and approved the decision to submit the manuscript for publication. The first draft of the manuscript was written by the first and last authors, with medical writing funded by the sponsor. The{q19} authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were at least 18 years of age (patients ≥12 years of age were eligible for the phase 2 trial) and had tumors harboring a *ROS1* fusion as identified {q20}by tissue-based local testing and as confirmed by a central diagnostic laboratory (see the Supplementary Appendix). All the patients from phase 1 and phase 2 who had at least one measurable target lesion, as prospectively confirmed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, were included in the efficacy analysis. Patients with measurable disease only in the CNS, as defined according to RECIST, version 1.1, could enroll; patients with asymptomatic metastases (treated or untreated) in the CNS were also allowed to enroll. *ROS1* resistance mutations were identified by {q21}either local tissue- or central plasma-based next-generation sequencing. Detailed descriptions of the eligibility criteria and of the biomarker assay methods are provided in the Supplementary Appendix.

In phase 2, patients with *ROS1* fusion–positive NSCLC were assigned to one of four cohorts: patients{q22} who had not previously received a ROS1 TKI, patients who had previously received one ROS1 TKI and had never received chemotherapy, patients who had previously received one ROS1 TKI and platinum-based chemotherapy, and patients who had previously received two ROS1 TKIs and had never received chemotherapy. For efficacy analyses, patients from phase 1 (all{q23} of whom had received repotrectinib at any dose) were pooled with patients from phase 2 on the basis of prespecified criteria to provide a robust sample of patients with this rare condition. The primary efficacy population included the cohort of patients who had not previously received a ROS1 TKI and the cohort of patients who had previously received one ROS1 TKI and had never received chemotherapy. The{q24} remaining two *ROS1* fusion–positive cohorts (which were not part of the primary efficacy population) included patients who

had received one ROS1 TKI and platinum-based chemotherapy and patients who had received two ROS1 TKIs and had never received chemotherapy.

The efficacy analysis population included all the patients with *ROS1* fusion–positive NSCLC who had started treatment with repotrectinib at any dose by October 15, 2021, with allowance for a minimum of approximately 14 months of follow-up (12-month{q25} duration of response follow-up) as of December 19, 2022 (data-cutoff date). The safety analysis population included all the patients who received treatment with the phase 2 dose, regardless of tumor or fusion type.

Trial End Points

The primary end points of the phase 1 trial were dose-limiting toxic effects, the maximum tolerated dose, and the recommended phase 2 dose of repotrectinib. The primary end point of the phase 2 trial was a confirmed objective response (complete{q26} or partial response) as assessed by blinded independent central review according to RECIST, version 1.1.

{q27}Secondary end points in the phase 2 trial included duration of response; clinical benefit; progression-free survival; overall survival; intracranial response as assessed by blinded independent central review according to modified RECIST, version 1.1, in patients with measurable brain metastases at baseline; safety as assessed with the use of the Common Terminology Criteria for Adverse Events, version 4.03; and patient-reported outcomes as assessed with the use of the European Organisation for Research and Treatment Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). The EORTC QLQ-C30 is a 30-item questionnaire consisting of a functional domain with five scales (physical, role, cognitive, emotional, and social), a symptom domain with three scales (fatigue, pain, and nausea and vomiting), a global health status–quality of life domain with one scale, and a single-item symptom domain with six scales (dyspnea, insomnia, appetite, constipation, diarrhea, and financial difficulties).[12] The{q28} response to each item is converted to a score ranging from 0 to 100 with the use of a standard scoring algorithm. A 10-point change from baseline {q29}in an item or domain score is considered to be clinically meaningful.[13,14]

Exploratory end points included confirmed response according to patient subgroup (age, sex, race, region, and Eastern Cooperative Oncology Group [ECOG] performance-status score [scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability]) and{q30} repotrectinib resistance alterations. Tumors were assessed at prespecified intervals until disease progression; in phase 2, brain imaging was performed during all tumor assessments regardless of whether brain metastasis was present at baseline. Additional details are provided in the Supplementary Appendix.

Statistical Analysis

The percentages of patients with a confirmed response and an intracranial response are reported, along with 95% confidence intervals calculated with the use of the two-sided 95% Clopper–Pearson method. Time-to-event end points

were estimated with the use of the Kaplan–Meier method, with 95% confidence intervals calculated by means of the Greenwood variance estimate. {q31} Descriptions of sample-size calculations, prespecified subgroup analyses, and time-to-event outcomes are provided in the Supplementary Appendix.

Results

Patients{q32}

From February 27, 2017, through December 19, 2022, we enrolled 520 patients. A total of 519 patients received one or more doses of repotrectinib (Fig. S2); 103{q33} patients were treated in phase 1, and 416 were treated in phase 2. Phase{q34} 1 doses, administration schedules, and dose-escalation data are provided in Table S1. Four dose-limiting toxic effects were observed in 2 patients who received 160 mg twice daily (grade 3 dizziness, dyspnea, and tissue hypoxia{q35}) and in 1 patient who received 240 mg once daily (grade 3 dizziness). The maximum tolerated dose was not reached. A dose of 160 mg once daily for 14 days, followed by 160 mg twice daily, was selected for phase 2. Rationales for dose selection and initial daily dose{q36} are provided in the Supplementary Appendix.

Of{q37} the 352 patients with *ROS1* fusion–positive NSCLC who received at least one dose of repotrectinib, 150 (43%) were still receiving treatment as of the data-cutoff date; the most common reason for discontinuation (in 106 patients [30%]) was disease progression. In{q38} the efficacy analysis population, 171 of the patients received at least one dose of repotrectinib and were followed for at least 14 months. Treatment exposure in{q39} these four cohorts, including the percentage of patients treated with the phase 2 dose of repotrectinib, is summarized in Table S2.

Activity in *ROS1* Fusion–Positive NSCLC

The primary efficacy population included 71 patients who had not previously received a ROS1 TKI and 56 patients who had previously received one ROS1 TKI and had never received chemotherapy (Table 1). The median age of the patients was 57 years in each cohort. The majority of these patients were women (61% of the patients who had not previously received a ROS1 TKI and 68% of those who had previously received one ROS1 TKI and had never received chemotherapy), had never smoked (63% and 64%, respectively), had stage 4 metastatic disease (94% and 98%), and had adenocarcinoma (97% and 95%); 24% and 46% of the patients, respectively, had brain metastasis at baseline as assessed by blinded central review.

A confirmed response occurred in 56 of the 71 patients (79%; 95% confidence interval [CI], 68 to 88) who had not previously received a ROS1 TKI; 7 patients (10%) had a complete response, and 49 (69%) had a partial response (Table 2 and Fig. 1A). The median time to response was 1.8 months (range, 0.9 to 5.6). The median follow-up was 24.0 months (range, 14.2 to 66.6), and the median duration of response was 34.1 months (95% CI, 25.6 to could not

be estimated) (Fig. S3A). An{q40} estimated 79% of the patients (95% CI, 68 to 90) had a response lasting at least 18 months. The median progression-free survival was 35.7 months (95% CI, 27.4 to could not be estimated) (Fig. 1B). At 18 months, the estimated progression-free survival was 70% (95% CI, 59 to 81). The estimated overall survival at 18 months was 88% (95% CI, 80 to 96) (Fig. S4A). The duration of treatment is shown in Fig. S5A. Of the 51 patients in this cohort who had never received chemotherapy, 82% (95% CI, 69 to 92) had a response (Table S4). A total of 63 patients were treated with the phase 2 dose; a response occurred in 78% (95% CI, 66 to 87) of the patients, and the estimated progression-free survival at 18 months was 70% (95% CI, 58 to 82) (Table S5 and Fig. S6A and S6B).

A confirmed{q41} response occurred in 21 of the 56 patients (38%; 95% CI, 25 to 52) who had previously received one ROS1 TKI and had never received chemotherapy; 3 patients (5%) had a complete response, and 18 (32%) had a partial response (Table 2 and Fig. 1C). The median time to response was 1.8 months (range, 1.6 to 3.6). The median follow-up was 21.5 months (range, 14.2 to 58.6), and the median duration of response was 14.8 months (95% CI, 7.6 to could not be estimated) (Fig. S3B). An{q42} estimated 56% of the patients (95% CI, 34 to 77) had a response lasting at least 12 months. The median progression-free survival was 9.0 months (95% CI, 6.8 to 19.6) (Fig. 1D). The estimated progression-free survival at 12 months was 41% (95% CI, 27 to 56). The median overall survival was 25.1 months (95% CI, 17.8 to could not be estimated) (Fig. S4B). The estimated overall survival at 12 months was 69% (95% CI, 56 to 82). Duration of treatment is shown in Figure S5B.

The{q43} ROS1 TKIs previously received by most of the patients who had previously received one ROS1 TKI and had never received chemotherapy were crizotinib (in 82%) and entrectinib (in 16%). A response occurred in 18 of the 46 patients (39%) who had previously received crizotinib and in 2 of the 9 patients (22%) who had previously received entrectinib (Table S6). The phase 2 dose was received by 53 of the patients; a response occurred in 38% (95% CI, 25 to 52), the median duration of response was 14.8 months (95% CI, 7.5 to could not be estimated), the median progression-free survival was 9.0 months (95% CI, 6.8 to 19.6), and the estimated progression-free survival at 12 months was 42% (95% CI, 28 to 57) (Fig. S6C and S6D).

We{q44} performed exploratory analyses to assess response in the primary efficacy population according to key subgroups. Table S7 shows the percentage of patients with a response according to age, sex, race, region, and ECOG performance-status score.

The{q45} characteristics of the patients at baseline in the two additional cohorts of the efficacy analysis population are summarized in Table S3. A confirmed{q46} response occurred in 11 of the 26 patients (42%) who had previously received one ROS1 TKI and chemotherapy, with a median duration of response of 7.4 months (95% CI, 4.4 to could not be estimated) (Fig. S7A and S7B). A confirmed response occurred in 5 of the 18 patients (28%) who

had previously received two ROS1 TKIs and had never received chemotherapy, with a median duration of response of 7.4 months (95% CI, 3.5 to could not be estimated) (Fig. S7C and S7D).

Subsequent{q47} therapies received by patients in the efficacy analysis population are summarized in Table S2. Of the 17 patients who had previously received at least one ROS1 TKI and had the *ROS1* G2032R mutation at baseline, 10 (59%; 95% CI, 33 to 82) had a confirmed response (Table S8 and Fig. S8).

Intracranial Activity in *ROS1* Fusion–Positive NSCLC

In{q48} the primary efficacy population, systemic (intracranial and extracranial) repotrectinib activity was observed in patients with measurable brain metastasis at baseline and in those without measurable brain metastasis at baseline (Table S9). Of the patients with measurable brain metastasis at baseline (in the phase 2 trial only), an intracranial response occurred in 8 of 9 (89%; 95% CI, 52 to 100) who had not previously received a ROS1 TKI and in 5 of 13 (38%; 95% CI, 14 to 68) who had previously received one ROS1 TKI and had never received chemotherapy. An{q49} estimated 83% (95% CI, 54 to 100) and 60% (95% CI, 17 to 100) of these patients, respectively, had an intracranial response lasting at least 12 months (Table 2 and Fig. 2A and 2B). Among the patients without brain metastasis at baseline, the estimated intracranial{q50} progression-free survival at 12 months was 91% (95% CI, 83 to 100) in the cohort with no previous receipt of a ROS1 TKI (54 patients) and 82% (95% CI, 65 to 98) in the cohort with previous receipt of one ROS1 TKI but no previous receipt of chemotherapy (30 patients) (Fig. 2C and 2D).

Repotrectinib Resistance

An exploratory analysis of paired samples of circulating tumor DNA obtained at baseline and after progression was performed. No *ROS1* resistance mutations emerged{q51} during the treatment period in the 14 patients with disease progression who had not previously received a ROS1 TKI. Five *ROS1* G2032R mutations and one *ROS1* L2086F mutation emerged during the treatment period in 6 of the 43 patients with disease progression who had previously received a ROS1 TKI; 2 of these 6 patients also had a *ROS1* mutation (F2004I or L2026M) at baseline (Table S10).

Safety

Among the 426 patients who were treated at the phase 2 dose, the most common treatment-related adverse events of any grade (categorized{q52} according to preferred terms in the *Medical Dictionary for Regulatory Activities* [MedDRA], version 21.0) were dizziness (in 58% of patients), dysgeusia (in 50%), and paresthesia (in 30%) (Table 3 and Table S11). Grade 3 or higher adverse events occurred in 122 patients (29%). The most common grade 3 or higher adverse events were anemia (in 4% of patients) and increased blood creatine kinase level (in 4%). Most{q53} adverse events (67%) were grade 1 or 2 in severity, and the most common adverse events (86%, of which 5% of the events were grade ≥3 in severity) were nervous system disorders. Grade 3 or

higher dizziness occurred in 11 patients (3%), and no patients discontinued repotrectinib therapy because of dizziness. Pneumonitis of any grade was uncommon, occurring in 11 patients (3%; grade ≥3 pneumonitis occurred in 1% of patients).

The{q54} median times to onset of the most common adverse events of special interest (composite terms) were 7 days (range, 1 to 526) for dizziness, 8 days (range, 1 to 589) for dysgeusia, and 14 days (range, 1 to 827) for paresthesia (Table S12). Adverse events of any grade and those of grade 3 or higher that occurred during the treatment period are listed in Table 3 and Table S13. The overall incidence of adverse events according to key subgroups (age, sex, race, region, and ECOG performance-status score) was consistent with the incidence in the overall population (Table S14).

Adverse events led to dose reduction in 163 patients (38%), to dose interruption in 213 (50%), and to treatment discontinuation in 31 (7%). The most common adverse event (categorized according to the preferred term in MedDRA, version 21.0) that led to dose reduction (in 11% of patients) or to dose interruption (in 8%) was dizziness. The most common adverse event that led to treatment discontinuation was pneumonitis (in 1% of patients). Fatal adverse events occurred in 19 patients (4%); none of the events were considered by the investigator to be related to the trial treatment (Table 3). Electrocardiograms in 398 patients showed no clinically significant effects on cardiac repolarization (as{q55} assessed by calculation of the corrected QT interval with the use of Fridericia's formula), heart rate, PR interval, or QRS duration.

Patient-Reported Outcomes

Among the 156 patients (63 patients who had not received a ROS1 TKI and 93 patients pooled from the three cohorts with previous receipt of a ROS1 TKI) with EORTC QLQ-C30 assessments, the percentage who completed each assessment was high (>86%) through cycle 12 and ranged from 64 to 100% between cycles 13 and 22. In the cohort with no previous receipt of a ROS1 TKI, the mean global health status score at baseline was 61.4{q56}, with a stable score (<10-point increase or decrease from baseline) or an improved score (≥10-point increase from baseline) in 65% of the patients at cycle 12 and a stable or improved score in 60% at cycle 22. In the pooled group with previous receipt of a ROS1 TKI, the mean{q57} global health status score at baseline was 58.2, with a stable or improved score in 71% of the patients at cycle 12 and a stable or improved score in 70% of those at cycle 22. A summary of the percentages of patients with stable, improved, or worsening global health status scores at cycles 12 and 22 is provided in the Supplementary Appendix. The mean changes in the global health status score between baseline and each cycle are shown in Figure S10.

Discussion

In this phase 1–2 trial, repotrectinib showed activity in patients with *ROS1* fusion–positive NSCLC. Among patients who had not received a ROS1 TKI, 79% had a response; the percentage of patients with a response remained high regardless of whether patients had previously received chemotherapy. Many responses were deep and occurred quickly, with a median time to response (1.8 months) coinciding with the first follow-up{q58} scan. The antitumor activity of repotrectinib appeared to be durable, with a median duration of response of 34.1 months and a median progression-free survival of 35.7 months. By comparison, entrectinib led to a median duration of response of 20.5 months and a median progression-free survival of 15.7 months,[8] and crizotinib led to a median duration of response of 24.7 months and a median progression-free survival of 19.3 months.[15]

Repotrectinib was likewise active in patients with *ROS1* fusion–positive NSCLC who had previously received a ROS1 TKI, a population in which approved TKIs have limited activity[2]; responses occurred in these patients regardless of which ROS1 TKI (crizotinib or entrectinib) they had previously received. Preclinical{q59} trials showed a response in 59% of patients with *ROS1* G2032R–mutant NSCLC, a finding that confirms the preclinical activity of repotrectinib against *ROS1* solvent-front mutations.[9,10] Other ROS1 TKIs, such as crizotinib, entrectinib, and lorlatinib, have not shown substantial activity against the G2032R{q60} mutation.[2-5] Additional research will be needed to determine the appropriate sequence in which targeted therapies are administered.

No *ROS1* resistance mutations emerged during the treatment period in patients with disease progression who had not received a ROS1 TKI. Although *ROS1* mutations emerged during the treatment period in 6 of the 43 patients with disease progression who had previously received a ROS1 TKI, these data should be interpreted with caution because of limitations in the sensitivity of the assays used for the detection of mutations. Additional research is needed to understand potential{q61} bypass mechanisms.

Repotrectinib was active against intracranial disease, a finding that was consistent with data from preclinical trials.[9,11] In{q62} each cohort, the percentage of patients with an intracranial response was generally similar to the percentage with a systemic response. In patients with measurable brain metastasis at baseline, the duration of the intracranial response was at least 12 months in 83% of the patients who had not previously received a ROS1 TKI and in 60% of those who had previously received 1 ROS1 TKI and had never received chemotherapy. Brain{q63} metastasis developed during the follow-up period in few of the patients without brain metastasis at baseline (intracranial progression-free survival at 12 months was estimated to be 91% in the cohort with no previous receipt of a ROS1 TKI and 82% in the cohort with previous receipt of 1 ROS1 TKI and no previous receipt of chemotherapy), which suggests that repotrectinib may delay or prevent the development of brain lesions. Overall,{q64} intracranial response rates with repotrectinib were numerically

higher than those seen with entrectinib in patients who had not previously received a ROS1 TKI and similar to those observed with lorlatinib therapy after previous receipt of crizotinib treatment, although cross-trial comparisons should be interpreted with caution.[8,16]

Adverse events related to repotrectinib therapy were primarily grade 1 or 2 in severity. Dizziness was the most common adverse event (in 58% of patients), but most of these events{q65} were low grade and were manageable with dose reductions or interruptions; discontinuation of repotrectinib therapy because of dizziness was not reported. Nervous system disorders such as dizziness and ataxia were expected consequences of repotrectinib; similar to entrectinib,[17] repotrectinib inhibits TRKA/B/C, which plays a role in the maintenance{q66} of the nervous system.[18] Overall, these neurologic adverse events were managed with supportive care measures that were {q67}recommended in the protocol and were similar to previously published guidance.[17]

This{q68} trial is limited by its single-group design and by its small sample size resulting from the rarity of *ROS1* fusion–positive NSCLC. Time-to-event efficacy end points and safety are continuing to be assessed to characterize long-term outcomes. Although other next-generation ROS1 inhibitors (e.g., taletrectinib and NVL-520) are in development,[19,20] this registrational trial of repotrectinib offers insights into the activity of next-generation, CNS-active ROS1 inhibitors.

Repotrectinib{q69} had durable activity and led to a response in a high percentage of patients with *ROS1* fusion–positive NSCLC, which included patients with tumors that had not been previously treated with a ROS1 TKI, tumors that had been previously treated with a ROS1 TKI, *ROS1* G2032R resistance mutations, and brain metastases. Repotrectinib therapy was mainly associated with low-grade adverse events. Side effects related to decreased TRK activity were as {q70}expected, a finding that was similar to that for other TKIs that inhibit TRK. Comparative trials may be needed to define the role of repotrectinib in the treatment sequence.

Data sharing

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.{q71}

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Financial disclosure

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.{q73}

Acknowledgments

We{q74} thank the participating patients and their families, who helped make this trial possible; the participating clinical trial teams; and Elaine Heatherington, PhD (of Bio Connections), for writing and editorial assistance with an earlier version of the manuscript.

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Quick Take Video

General comments on video or navigation (use sticky notes and include timecode):

Repotrectinib for *ROS1*-Fusion Lung Cancer

DOI: NEJMdo007352

View video and metadata on JW Player (https://content.jwplatform.com/previews/)

Multimedia Blurb

Repotrectinib for *ROS1* Fusion–Positive Lung Cancer

In many patients with *ROS1* fusion–positive non–small-cell lung cancer who receive currently approved ROS1 tyrosine kinase inhibitors, resistance mutations occur. New research findings on a next-generation ROS1 TKI are summarized in a short video.

Marginal note for print

A Quick Take is available at NEJM.org

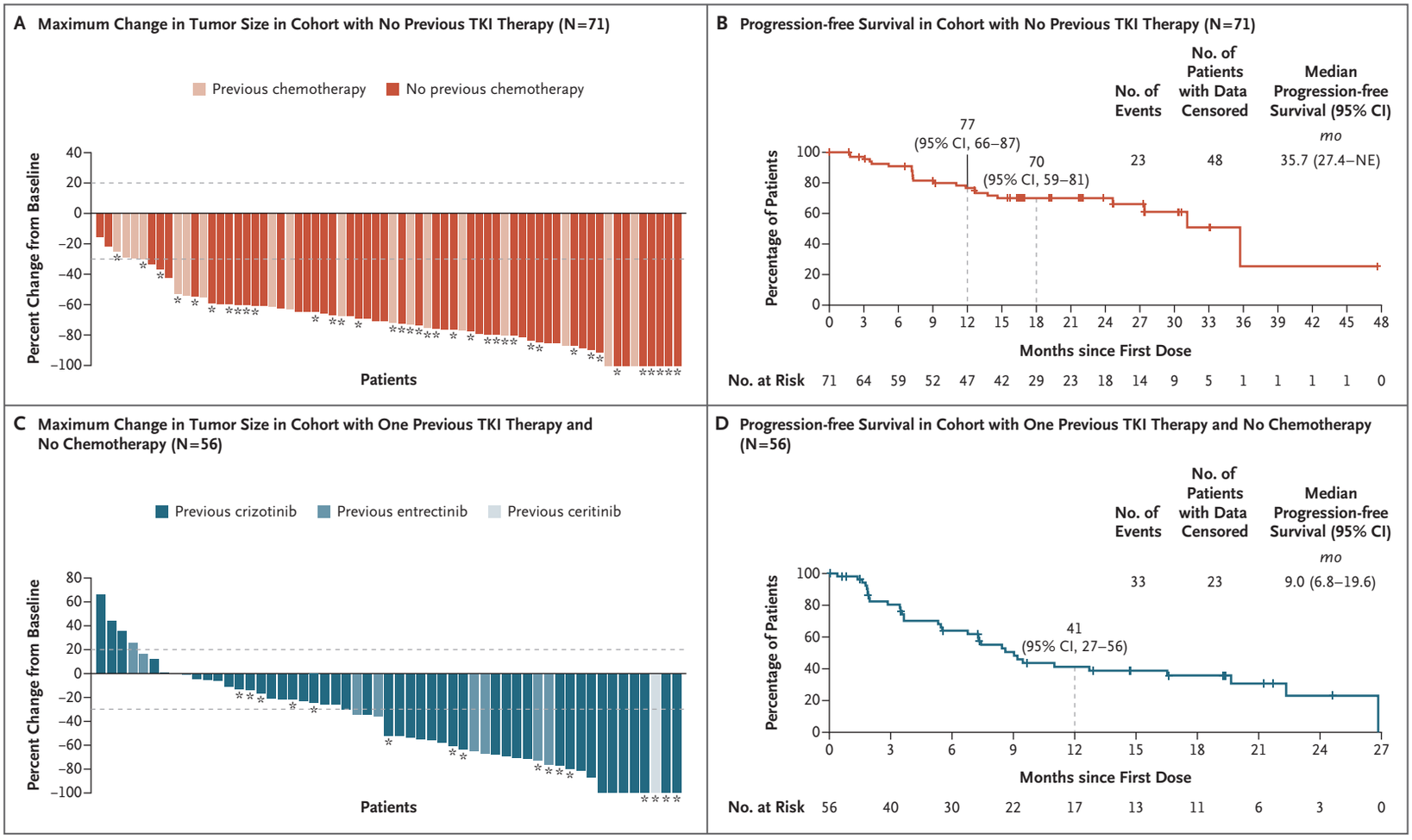

Figure 1. Efficacy of Repotrectinib in the Primary Efficacy Population.

Shown are the change in the tumor burden (Panel A) and progression-free survival (Panel B) in 71 patients (8 patients{q75} from phase 1 and 63 from phase 2) who had not previously received an ROS1 tyrosine kinase inhibitor (TKI) and the change in the tumor burden (Panel C) and progression-free survival (Panel D) in 56 patients (3 patients from phase 1 and 53 from phase 2) who had previously received one ROS1 TKI and had never received chemotherapy. In Panels A and C, the waterfall plots include only patients with baseline and postbaseline target-lesion measurements at baseline and during follow-up; asterisks indicate that treatment is ongoing. In Panels B and D, tick marks indicate censored data. NE denotes could not be estimated.

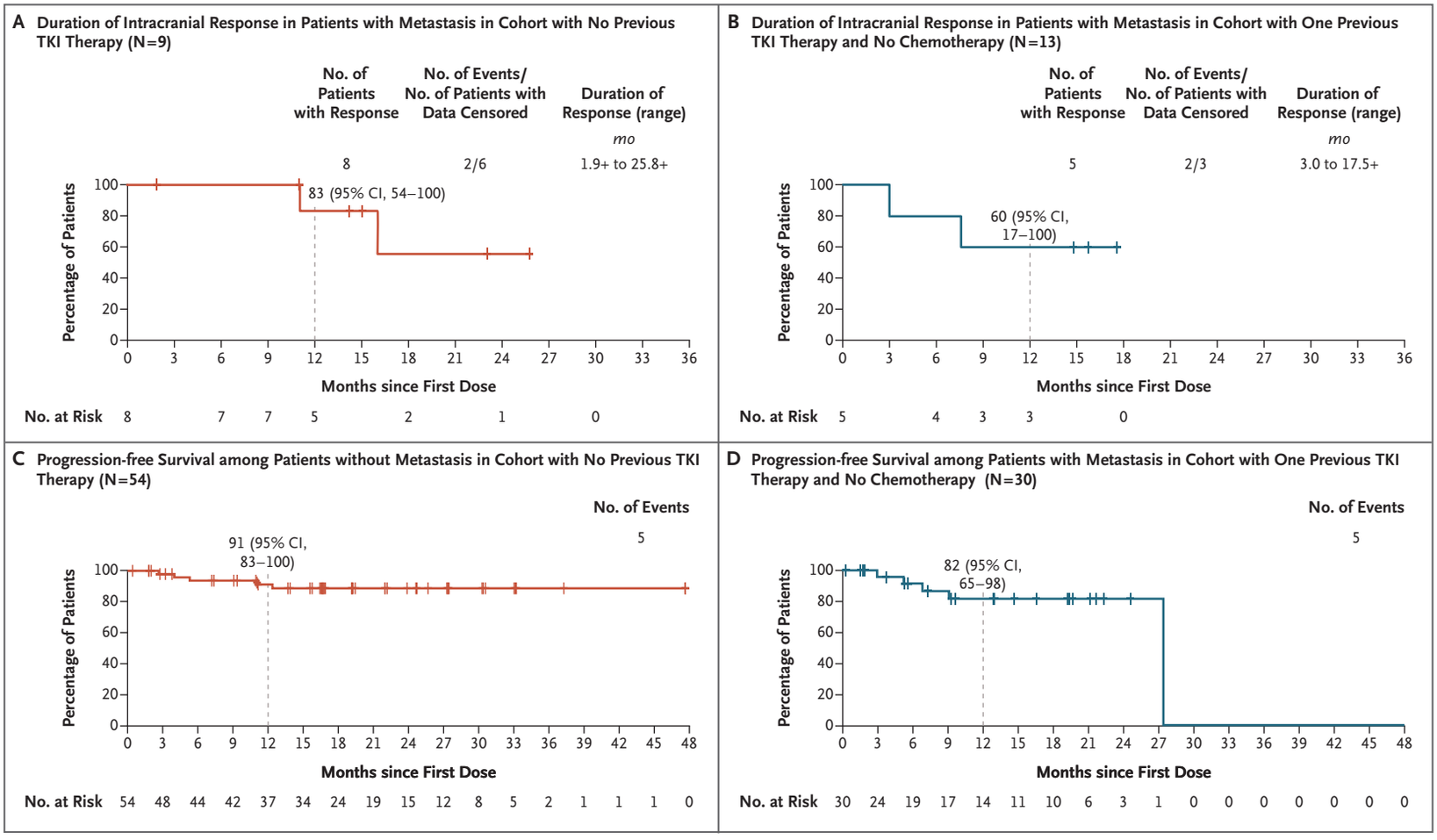

Figure 2. ***ROS1*** **G2032R and Intracranial Efficacy.**{q76}

Shown is the duration of intracranial response in 9 patients with measurable brain metastasis at baseline who had not previously received a ROS1 TKI (Panel A) and in 13 patients who had previously received one ROS1 TKI and had never received chemotherapy (Panel B). Intracranial progression-free survival in 54 patients (6 patients from phase 1 and 48 from phase 2) without brain metastases at baseline who had not previously received a ROS1 TKI (Panel C) and in 30 patients (3 patients from phase 1 and 27 from phase 2) who had previously received one ROS1 TKI and had never received chemotherapy (Panel D) is shown. The analysis of intracranial progression-free survival was exploratory and was based on the time to the development of new brain lesions as assessed by blinded independent central review. A plus sign on values for duration of response indicates an ongoing response. In all panels, tick marks indicate censored data.

Table 1. Characteristics of the Patients at Baseline (Primary Efficacy Population).*

Characteristic	No Previous TKI (N=71)†	One Previous TKI and No Chemotherapy (N=56)‡
Age		
Median (range) — yr	57 (28–80)	57 (33–78)
Distribution — no. (%)		
≥18 to 64 yr	52 (73)	41 (73)
≥65 yr	19 (27)	15 (27)
Sex — no. (%)		
Female	43 (61)	38 (68)
Male	28 (39)	18 (32)
Geographic region — no. (%)		
United States	11 (15)	17 (30)
Asia	41 (58)	23 (41)
Other§	19 (27)	16 (29)
ECOG performance-status score — no. (%)¶		
0	24 (34)	18 (32)
1	47 (66)	38 (68)
Stage 4 metastatic disease — no. (%)	67 (94)	55 (98)
Adenocarcinoma — no. (%)	69 (97)	53 (95)
Smoking history — no. (%)		
Never smoked	45 (63)	36 (64)
Current smoker	2 (3)	1 (2)
Former smoker	16 (23)	16 (29)
Brain metastasis — no. (%)‖		
Yes	17 (24)	26 (46)
No	54 (76)	30 (54)
No. of previous lines of systemic therapy — no. (%)		
0	51 (72)	0
1	16 (23)	56 (100)
2	2 (3)	0
≥3	2 (3)	0
No. of previous lines of chemotherapy with or without immunotherapy — no. (%)		
0	51 (72)	NA
1	17 (24)	NA
2	2 (3)	NA
≥3	1 (1)	NA
No. of previous lines of immunotherapy alone — no. (%)		
0	69 (97)	NA
1	2 (3)	NA
Previous ROS1 TKI therapy — no. (%)		
Crizotinib	NA	46 (82)
Entrectinib	NA	9 (16)
Ceritinib	NA	1 (2)

* The primary efficacy population included patients with ROS1 fusion–positive non–small-cell lung cancer who had not previously received a ROS1 tyrosine kinase inhibitor (TKI) and those who had previously received one ROS1 TKI and had never received chemotherapy. NA denotes not applicable.
† The cohort of patients who had not previously received a ROS1 TKI included 8 patients from phase 1 and 63 patients from phase 2.
‡ The cohort of patients who had previously received one ROS1 TKI and had never received chemotherapy (or immunotherapy) included 3 patients from phase 1 and 53 patients from phase 2.
§ Other regions included Australia, Canada, and Europe.
¶ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
‖ Brain metastasis at baseline was confirmed by blinded independent central review.

Table 2. Response to Repotrectinib (Primary Efficacy Population).*{q82}

Variable	No Previous TKI (N=71)	One Previous TKI and No Chemotherapy (N=56)
Objective response†		
No. of patients with response	56	21
Percentage of patients with response (95% CI)	79 (68–88)	38 (25–52)
Median time to response (range) — mo	1.8 (0.9–5.6)	1.8 (1.6–3.6)
Median duration of response (95% CI) — mo	34.1 (25.6–NE)	14.8 (7.6–NE)
Best overall response — no. (%)‡		
Complete response	7 (10)	3 (5)
Partial response	49 (69)	18 (32)
Stable disease	11 (15)	23 (41)
Progressive disease	2 (3)	9 (16)
Not evaluable	0	2 (4)
Clinical benefit§		
No. of patients with benefit	67	44
Percentage of patients with benefit (95% CI)	94 (86–98)	79 (66–88)
Median progression-free survival (95% CI) — mo	35.7 (27.4–NE)	9.0 (6.8–19.6)
Median overall survival (95% CI) — mo	NE (44.4–NE)	25.1 (17.8–NE)
Intracranial objective response¶		
No. of patients with measurable brain metastases at baseline	9‖	13**
No. of patients with response	8	5
Percentage of patients with response (95% CI)	89 (52–100)	38 (14–68)
Complete response — no. (%)	1 (11)	0
Partial response — no. (%)	7 (78)	5 (38)
Median duration of response (95% CI) — mo	NE (16.0–NE)	NE (3.0 to NE)

* NE{q83} denotes could not be estimated.
† Objective response (complete or partial response) was assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
‡ Response was assessed by blinded independent central review according to RECIST, version 1.1.
§ Clinical benefit, defined as a best overall response of confirmed complete response, confirmed partial response, or stable disease as assessed by blinded independent central review according to RECIST, version 1.1, was a prespecified secondary end point.
¶ Response was assessed by blinded independent central review according to modified RECIST, version 1.1.
‖ Response in one patient could not be evaluated because brain{q84} imaging was not performed after baseline. A partial response occurred in the two patients who underwent an intervention for central nervous system lesions within 60 days before enrollment.
** A partial response occurred in two of seven patients who underwent an intervention for central nervous system lesions within 60 days before enrollment.

Table 3. Adverse Events in the 426 Patients Who Received the Phase 2 Dose of Repotrectinib.*

Event	During Treatment Period		Related to Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	422 (99)	216 (51)	409 (96)	122 (29)
Event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (38)	1 (<1)	111 (26)	0
Anemia	160 (38)	33 (8)	111 (26)	16 (4)
Paresthesia	143 (34)	3 (1)	126 (30)	3 (1)
Dyspnea	117 (27)	27 (6)†	36 (8)	2 (<1)
Increased alanine aminotransferase level	99 (23)	8 (2)	76 (18)	6 (1)
Fatigue	95 (22)	4 (1)	70 (16)	3 (1)
Ataxia	90 (21)	1 (<1)	87 (20)	0
Increased aspartate aminotransferase level	89 (21)	9 (2)	75 (18)	6 (1)
Nausea	85 (20)	3 (1)	51 (12)	2 (<1)
Muscular weakness	85 (20)	8 (2)	59 (14)	6 (1)
Headache	79 (19)	0	42 (10)	0
Increased blood creatine kinase level	75 (18)	15 (4)	72 (17)	15 (4)
Weight increase	67 (16)	11 (3)	49 (12)	7 (2)
Memory impairment	65 (15)	1 (<1)	54 (13)	1 (<1)
Cough	64 (15)	1 (<1)	10 (2)	0
Event that led to treatment discontinuation	31 (7)	—{q85}	14 (3)	—
Event of any grade that led to dose reduction	163 (38)	—	149 (35)	—
Event of any grade that led to dose interruption	213 (50)	—	150 (35)	—
Any serious event	147 (35)	—	38 (9)	—
Death	19 (4)	—	0	—

* A repotrectinib dose of 160 mg once daily for 14 days, followed by 160 mg twice daily, was assessed in the phase 2 trial. Adverse events were categorized according to preferred terms of the *Medical Dictionary for Regulatory Activities,* version 21.0, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

† Two{q86} patients (<1%) had grade 5 dyspnea.

Queries

q1. AU: Your article has been edited for grammar, consistency, readability, adherence to Journal style, and clarity for nonspecialist readers. To expedite publication, we do not ask authors for specific approval of routine changes; please read the entire article to make sure your meaning has been retained. Note that we may be unable to make changes that conflict with Journal style or create grammatical or other problems. Finally, please note that a delayed or incomplete response may delay publication of your article. Thank you!

q2. AU: Okay to publish postal and e-mail addresses?

q3. AU: Please confirm that none of the material in the Supplementary Appendix is under copyright by a third party.

q4. AU: Please confirm that all the numbers and terms in the abstract also appear in the body of the article (in the text or in a table or figure).

q5. AU: (A) To save space, only first/middle initials and surnames will appear on the Abstract page. Lists of full names, degrees, and affiliations will appear in an Appendix at the end of the article. Please confirm. (B) The M.S. degree for Dr. Beg has been deleted per our style. Please confirm.

q6. AU: (A) RECIST and BICR removed because of spatial constraints. Please confirm. (B) Please clarify "and antitumor activity analysis combined phase 1 and 2 results." Do you mean "and efficacy analyses included patients from phase 1 and phase 2"?

q7. AU: Please verify all dosage information, here and throughout the article, making sure that the numbers, units, frequencies, routes of administration, and durations are correct.

q8. AU: Please verify trial registration number(s).

q9. AU: This blurb was drafted for use at NEJM.org by the deputy editor and has been edited to reflect wording in the edited manuscript. Please confirm its accuracy. Note that we are limited to approximately 200 characters and spaces and that any substantive changes will require approval by the deputy editor.

q10. AU: OK to change to "such as the G2032R mutation in the solvent front of the kinase domain"?

q11. AU: Sentence OK?

q12. AU: (A) Please clarify "improved CNS coverage" (do you mean "Although entrectinib reaches a higher concentration than crizotinib in the CNS"?). (B) Change to "only 11% of patients...response to entrectinib" OK?

q13. AU: Changes to sentence OK?

q14. AU: Change to "is an ongoing international" (or do you mean "was an international...")?

q15. AU: Sentence has been split to avoid single-sentence paragraph.

q16. AU: Change to "all the enrolled patients were assigned to receive repotrectinib" OK (per the Supplementary Appendix, one enrolled patient did not actually receive the drug).

q17. AU: "appropriate" OK?

q18. AU: (A) Do you mean "data and safety monitoring committee"? (B) Changes to sentence "All the authors participated..." OK?

q19. AU: New sentence inserted per our policy. Please confirm.

q20. AU: Do you mean "as identified by the analysis of tumor tissue at a local laboratory"?

q21. AU: Do you mean "were identified by next-generation sequencing analysis of tumor tissue at a local laboratory or plasma at a central laboratory"?

q22. AU: Cohorts correct as described?

q23. AU: (A) Insertion of "all of whom" correct? (B) Change to "a robust sample of patients with this rare condition" OK?

q24. AU: This sentence appears to be unnecessary. OK to remove?

q25. AU: Do you mean "to permit assessment of the percentage of patients with a duration of response of ≥12 months"?

q26. AU: Insertion of "(complete or partial response)" OK?

q27. AU: Paragraph breaks in this subsection OK?

q28. AU: (A) New sentence OK? (B) Please specify the range of possible scores and how the scores are interpreted (e.g., do higher scores indicate more severe disease? improved global health status?).

q29. AU: Please give a brief summary of how often the questionnaire was completed ("cycles" are mentioned below) and provide the time point used to measure the change from baseline.

q30. AU: (A) Subgroups correct as specified? Sex was included per Table S7. (B) Please clarify "repotrectinib resistance alternations" (do you mean "emergence of repotrectinib resistance mutations during the treatment period"?).

q31. AU: Please confirm whether insertion of the following (per Journal requirements for statistical reporting) is appropriate: "The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing."

q32. AU: New subsection heading OK?

q33. AU: Please confirm 103 patients. Per the first row in Table S1, 93 patients received treatment in phase 1.

q34. AU: Sentence OK?

q35. AU: "tissue hypoxia" correct? Or do you mean "hypoxemia"

q36. AU: "initial daily dose" correct?

q37. AU: New location of paragraph OK?

q38. AU: Change to "in the efficacy analysis population" correct?

q39. AU: Change to "in these four cohorts" correct?

q40. AU: Sentence OK?

q41. AU: Sentence OK?

q42. AU: Sentence OK?

q43. AU: Paragraph break and new location of sentence OK?

q44. AU: Paragraph break and division of sentence into two sentences (to avoid single-sentence paragraph) OK?

q45. AU: Sentence OK?

q46. AU: Both sentences beginning "A confirmed response..." correct?

q47. AU: Sentence OK?

q48. AU: Change to "In the primary efficacy population" correct?

q49. AU: Sentence OK, include removal of Fig. S9 citation (sentence doesn't appear to show data provided in this figure)?

q50. AU: Please clarify "intracranial progression-free survival" here and in Figure 2 legend.

q51. AU: Changes to "emerged during the treatment period" correct in this paragraph? Our style is to use "emergent" to mean "urgent."

q52. AU: Text in parentheses OK?

q53. AU: Correct that units in this sentence are AEs and not patients? Please specify numerators and denominators used to calculate 67%, 86%, and 5%.

q54. AU: (A) Paragraph break OK? (B) Please clarify "composite terms."

q55. AU: Text in parentheses OK?

q56. AU: Rounding of scores to nearest tenth (61.4 and 58.2) OK?

q57. AU: (A) Insertion of "mean" OK? (B) Changes to sentence "A summary..." OK? If not, please clarify "breakdown."

q58. AU: "follow-up scan" correct?

q59. AU: Sentence OK?

q60. AU: (A) Change to "G2032R mutation" correct? (B) Change to sentence "Additional research..." OK?

q61. AU: Please clarify "potential bypass mechanisms."

q62. AU: Sentence OK?

q63. AU: Sentence OK?

q64. AU: Do you mean: "Overall, the percentage of patients with an intracranial response who had not previously received a ROS1 TKI was higher among those who received repotrectinib than among those who received entrectinib, and the percentage of patients with an intracranial response who had previously received crizotinib was similar among those who received repotrectinib and those who received lorlatinib; however, cross-trial comparisons should be interpreted with caution."

q65. AU: Change to "most of these events" (meaning most of the dizziness events) OK?

q66. AU: Please clarify "maintenance."

q67. AU: Change to "measures that were recommended in the protocol and were similar" OK?

q68. AU: Sentence OK?

q69. AU: Sentence OK?

q70. AU: "were as expected" correct?

q71. AU: The final page of this proof is the data sharing statement for your article. The statement was generated from your responses to questions asked by our system during the manuscript submission process. The PDF statement will be posted along with your article at NEJM.org. Please confirm that it is accurate.

q72. AU: Please verify source(s) of funding.

q73. AU: Please confirm that the disclosure forms you submitted are accurate, complete, and current for each author. If any of the information changes before publication, please update the forms.

q74. AU: Acknowledgments OK as edited?

q75. AU: (A) Insertions of numbers of patients from phase 1 and phase 2 OK? (B) Please define the dashed lines in Panels A and C.

q76. AU: (A) Please clarify "ROS1 G2032R" in title (or do you mean "Intracranial Efficacy in the Primary Efficacy Population"?). (B) Definition of plus signs correct?

q77. AU: To reduce table length, OK to present data for female sex only?

q78. AU: When appropriate, percents have been revised per Journal rounding style.

q79. AU: To reduce table length, OK to remove "No" row?

q80. AU: Do you mean "...immunotherapy without chemotherapy"?

q81. AU: Footnotes OK?

q82. AU: Title OK?

q83. AU: Footnotes OK?

q84. AU: "because brain imaging was not performed after baseline" correct?

q85. AU: Should the dashes be replaced with "0"? With "NA"?

q86. AU: Were these events related to treatment?

Running head

Repotrectinib in *ROS1* Fusion–Positive NSCLC

TWeek blurb

Repotrectinib in *ROS1* Fusion–Positive Lung Cancer

{q9}In this phase 1–2 trial, the tyrosine kinase inhibitor repotrectinib led to objective response in 79% of patients with *ROS1* fusion–positive NSCLC. The median progression-free survival was nearly 3 years.

Social media image

Ad is Figure 1B

NEJM Topics

Hematology/Oncology
Lung Cancer
Treatments in Oncology

Data Sharing Statement

Drilon A, Camidge DR, Lin JJ, et al. Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer. N Engl J Med. DOI: 10.1056/NEJMoa2302299.

Question	Authors' Response
Will the data collected for your study be made available to others?	No
Would you like to offer context for your decision?	Bristol Myers Squibb company policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html
Which data?	—
Additional information about data	—
How or where can the data be obtained?	—
When will data availability begin?	Beginning Date:
When will data availability end?	End Date:
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—
When will supporting documents availability begin?	Beginning Date:
When will supporting documents availability end?	End Date:
To whom will data be available?	—
For what type of analysis or purpose?	—
By what mechanism?	—
Any other restrictions?	—
Additional information	—

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